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Fluid balance and outcome in cardiac arrest patients admitted to intensive care unit

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Abstract

Background Although shock following cardiac arrest is common and contributes significantly to mortality, the influence of the modalities used to manage the hemodynamic situation, particularly with regard to fluid balance, remains unclear. We evaluated the association between positive fluid balance and outcome after out-of-hospital cardiac arrest (OHCA).

Methods We conducted a multicenter study from August 2020 to June 2022, which consecutively enrolled adult OHCA patients in 17 intensive care units. The primary endpoint was 90-day survival. Multivariate Cox analysis, propensity score matching and landmark analysis were performed, along with several sensitivity analyses.

Results Of the 816 patients included in our study, 74% had a positive fluid balance, and 291 of 816 patients (36%) were alive at 90-day. A positive fluid balance was associated with mortality after adjusted multivariate analysis (HR = 1.8 [1.3 – 2.3], $p < 0.001$), after propensity score matching (n = 193 matched patient pairs, HR = 1.6 [1.1 – 2.1], $p = 0.005$) and after landmark analysis. We reported a dose-dependent association between fluid balance and mortality. Patients with a positive fluid balance were more likely to need renal replacement therapy (10% *vs.* 2%, $p = 0.001$) and had a lower minimum P_aO_2/F_iO_2 ratio in the first seven days (158 *vs.* 180, $p < 0.001$).

Conclusions After cardiac arrest, a positive fluid balance is consistently associated with a worse outcome. Pending further data, a restrictive fluid therapy strategy may be beneficial in post-OHCA patients.

Trial registration: ClinicalTrial.gov cohort AfterROSC-1 NCT04167891 registered November 13th, 2019, ethics committees 2019-A01378-49 and CPP-SMIV 190901.

Keywords Out-of-hospital cardiac arrest, Epidemiology, Fluid balance, Outcome

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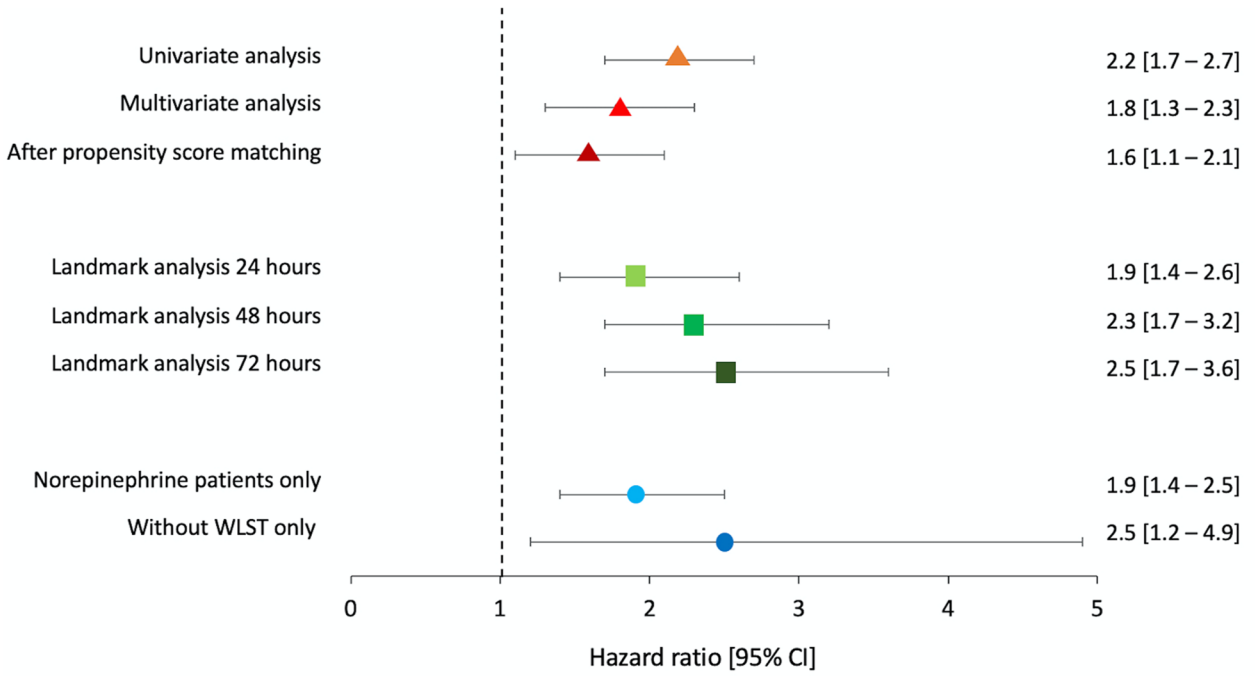
Graphical abstract



Association between a positive fluid balance and 90-day mortality after OHCA after different survival analyses

CI: confidence interval, OHCA: Out-of-Hospital Cardiac Arrest, WLST: Withdrawal of Life Sustaining Therapy

Background

Among patients admitted to the intensive care unit (ICU) following out-of-hospital cardiac arrest (OHCA), the prognosis remains poor, with approximately two-thirds not surviving their hospital stay(1,2). A significant proportion of post-cardiac arrest patients develop multiorgan dysfunction following ischaemia–reperfusion injury, systemic inflammatory responses, and haemodynamic instability, accounting for up to 35% of deaths in this setting(2–4).

Fluid therapy plays a critical role in early haemodynamic support(5). In post-cardiac arrest care, achieving a balance between adequate resuscitation and avoiding fluid overload is particularly challenging. Current guidelines for post-cardiac arrest care provide general recommendations for haemodynamic management but highlight the limited evidence for optimal fluid therapy in these patients(5). Notably, a positive fluid balance is associated with poor outcomes in several critically ill groups, including those with sepsis and acute respiratory distress syndrome(6,7). Discordant findings between observational studies and randomized trials may be partly due to indication bias, as higher cumulative fluid balances often indicate greater severity of illness(6). To date, there is no specific data available regarding fluid management in cardiac arrest patients.

Accordingly, we conducted a study within a multicenter cohort of ICU patients resuscitated from OHCA, including a detailed analysis to adjust for patient severity. Our aim was to evaluate the association between positive fluid balance and outcomes after cardiac arrest.

Methods

This study was conducted according to the Strengthening The Reporting of OBservational studies in Epidemiology guidelines, and the cohort was registered on ClinicalTrials.gov before the first patient was enrolled (Cohort AfterROSC-1, NCT04167891, registered November 13th, 2019)(8). The research protocol was approved by the relevant ethics committees (2019-A01378-49; CPP-SMIV 190901) and the French data protection authorities, according to the principles of the Declaration of Helsinki.

Study Setting and population

The AfterROSC Network includes ICUs in public or private university- or non-university hospitals in France and Belgium. AfterROSC prospectively collects data from adult OHCA patients admitted to ICUs of the network starting August 1, 2020(9,10). This nested study was conducted in 17 ICUs, and included patients admitted after OHCA between August 2020 and June 2022.

Study population

All patients admitted to the participating centers after OHCA were screened for participation. Patients were eligible if they were 18 years or older, admitted to the ICU after OHCA, and remained comatose at admission (Glasgow Coma Scale ≤ 8). Exclusion criteria were in-hospital cardiac arrest, patients under guardianship, and those previously included in the AfterROSC registry. Patients with incomplete data regarding the primary endpoint (survival on day 90) were not included in the analysis and were considered as *missing at random.*

OHCA management

In France, OHCA is managed according to international guidelines by an emergency team that includes at least one physician trained in emergency medicine(11). Patients who achieve return of spontaneous circulation (ROSC) on the field are then transferred to the ICU, where care may include targeted temperature management according to current guidelines(5). Post-cardiac arrest shock management involves fluid resuscitation and the use of vasoactive agents, primarily norepinephrine(12), along with epinephrine and dobutamine, administered at the physician's discretion. Fluid responsiveness protocol was not standardized.

Data collection

All data were collected by a dedicated study nurse or investigator at each participating center. All demographic and arrest-related data were collected according to Utstein style(13). General data included demographic characteristics, comorbidities, location and cause of OHCA. Data collected on pre-hospital care included bystander presence, bystander cardiopulmonary resuscitation (CPR), defibrillation before advanced life support, epinephrine administration and dose (total dose administered by emergency medical services during advanced life support), time from arrest to initiation of CPR, and time from CPR to ROSC.

Admission data were Simplified Acute Physiology Score (SAPS) II, Charlson and Sepsis-related Organ Failure Assessment (SOFA) scores, haemoglobin level, arterial pH and lactate level. The CAHP (Cardiac Arrest Hospital Prognosis) score was calculated using the previously published formula(14,15). Hospital care data were recorded for targeted temperature management, maximum SOFA during the 3 first days, maximum vasoactive inotropic score (VIS)(16) during the first 3 days (calculated according to the formula: VIS = 100 * epinephrine (µg/kg/min) + 100 * norepinephrine (µg/kg/min) + dobutamine (µg/kg/min)) and renal replacement therapy.

Daily fluid intake was calculated for the first 7 days, considering only crystalloid solutions since no colloids were used in participating centers. Cumulative fluid balance(17) was defined as the difference between cumulative fluid inputs (intravenous medications, fluid boluses, blood products, enteral and parenteral nutrition, and maintenance fluids) and cumulative fluid outputs (urine output, ultrafiltration in case of dialysis and surgical drains). A positive fluid balance was defined as a fluid balance strictly positive (i.e., greater than 0 ml) on day 7 (if the patient was still hospitalized) or at the time of discharge or death, whereas a negative fluid balance was defined as a fluid balance strictly negative (i.e., less than 0 ml). It was calculated from ICU admission until day 7, death, or discharge (whichever came first) and was categorized as either positive or negative.

Endpoints

The primary endpoint was survival on day 90.

Secondary endpoints were use of renal replacement therapy, minimum P_aO_2/F_iO_2 ratio during the first 7 days in the ICU, duration of mechanical ventilation and ventilator-free days (up to day 28), duration of catecholamine use, length of ICU stay, and ICU-free days (up to day 28).

Statistical analysis

Data are reported as medians and interquartile ranges (IQRs) for continuous variables and as percentages for qualitative variables. We compared categorial variables using the Pearson chi-square test or Fisher test, as appropriate and continuous variables by the Student t test or the Wilcoxon-Mann–Whitney test as appropriate. Linearity of quantitative variables was assessed using fractional polynomial regression. In the absence of linearity, the variables were dichotomized based on the median and included in the model as such.

Univariate analysis comparing survivors and non-survivors at day 90 was conducted using Kaplan–Meier curves and log-rank tests. Variables with a p-value < 0.15 in univariate analysis were then included in a full multivariable model. Finally, a restricted model was derived using a backward stepwise multivariable Cox regression.

Additional analyses were performed to strengthen our findings:

1. Given the potential for indication bias (i.e., patients with a positive fluid balance may be sicker than those with a negative fluid balance), a propensity score was developed based on pretreatment characteristics to identify variables associated with a positive fluid balance. Survival at 90 days was then compared using multivariate Cox regression after matching on the propensity score in a 1:1 manner.
2. To address potential immortal time bias (i.e., fluid balance is typically positive in the initial days and becomes negative later, meaning that patients who die early may not survive long enough to achieve a negative fluid balance), we performed several landmark analyses. We compared survival rates by fluid balance status (defined by a positive or negative cumulative fluid balance), conditional on survival to specific time points, by excluding those who died within the first 24, 48, or 72 h.
3. Additional analyses were performed in different subgroups according to the severity predicted by the CAHP score[9, 14] (low risk (score ≤ 150), intermediate risk (score 150—200) and high risk (score ≥ 200)), in patients treated with norepinephrine alone (excluding those who received other vasopressors) and in patients without withdrawal of life sustaining therapy (WLST).
4. A sensitivity analysis was conducted using unfavorable neurological outcome (modified Rankin Scale between 4 and 6) at day 90 as the endpoint, instead of survival
5. Finally, to explore a potential dose–response relationship, we compared patients according to negative fluid balance and tertiles of positive fluid balance and used a trend test.

Missing data were managed using case-complete analysis. All tests were two-sided, with $p < 0.05$ considered statistically significant. Analyses were performed using STATA16.1 software (College Station, TX, USA).

Results

From August 2020 to June 2022, 925 patients were eligible, of whom 816 were included in this study (Fig. 1). Comparison of included (n = 816) and excluded (n = 109) patients is shown in Supplementary file 1. Their characteristics are detailed in Table 1. 576 (71%) patients were male, with a median age of 65 years. 74% of the population had a cumulative positive fluid balance in the first seven days. The median times from collapse to CPR and from CPR to ROSC were 3 and 20 min, respectively. The median CAHP score for the cohort was 167. Patients with a positive fluid balance had a greater severity of illness than those with a negative fluid balance, as indicated by an initial lactate level of 4.6 mmol/L (*vs.* 3.1 mmol/L, $p < 0.001$), a maximal VIS of 51 (*vs.* 22, $p < 0.001$) and a maximal SOFA of 11 (*vs.* 10, $p < 0.001$).

Fluid intake and balance

In this cohort, the median fluid intake in the first seven days was 2500 [1000 – 5000] milliliters (mL), and the median cumulative fluid balance in the first seven days was 2291 [- 87 to 5814] mL. Figure 2 shows the daily

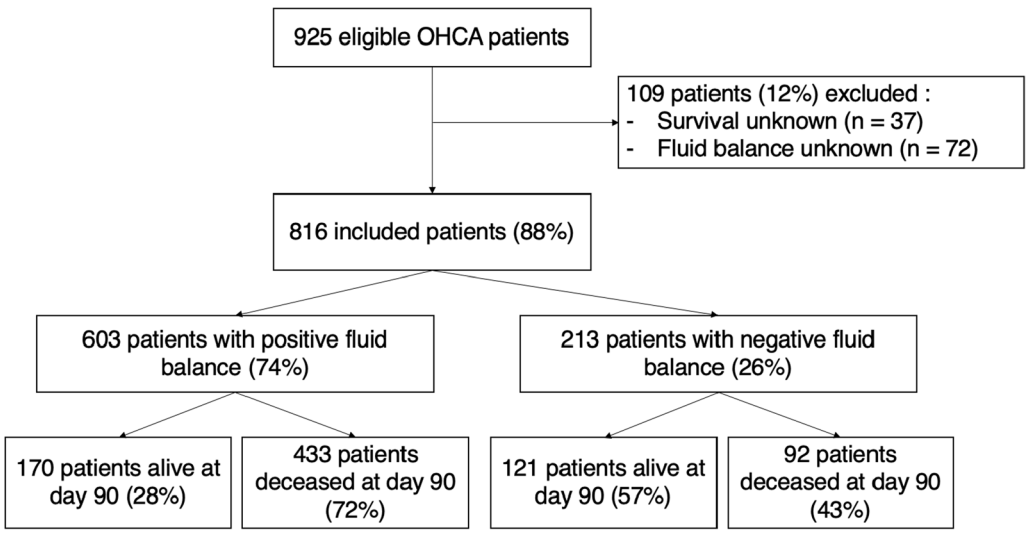

925 eligible OHCA patients
109 patients (12%) excluded :
- Survival unknown (n = 37)
- Fluid balance unknown (n = 72)
816 included patients (88%)
603 patients with positive fluid balance (74%)
213 patients with negative fluid balance (26%)
170 patients alive at day 90 (28%)
433 patients deceased at day 90 (72%)
121 patients alive at day 90 (57%)
92 patients deceased at day 90 (43%)

Fig. 1 Patient flow chart. *OHCA* out-of-hospital cardiac arrest

Table 1 Patients demographic and Utstein characteristics, characteristics at admission and primary care according to cumulative fluid balance

	Total population (n = 816)	Positive fluid balance (n = 603)	Negative fluid balance (n = 213)	*p*
Age, years, median [IQR]	62 [52 – 72]	63 [52 – 72]	61 [51 – 71]	0.26
Male, n (%)	576 (71)	420 (70)	156 (73)	0.32
Comorbidities, n (%): Cardiovascular disease Diabetes Respiratory disease Cancer Chronic renal failure Liver disease	227 (28) 136 (17) 97 (12) 72 (9) 38 (5) 18 (2)	171 (28) 105 (17) 78 (13) 54 (9) 28 (5) 14 (2)	56 (26) 31 (15) 19 (9) 18 (8) 10 (5) 4 (2)	0.56 0.34 0.12 0.82 0.98 1.00
At home, n (%)	518 (63)	382 (63)	136 (64)	0.90
Bystander-witnessed, n (%)	677 (83)	508 (84)	169 (80)	0.13
Bystander CPR, n (%)	544 (68)	398 (67)	146 (70)	0.50
Shockable rhythm, n (%)	375 (47)	266 (45)	109 (52)	0.07
Epinephrine administered, mg, median [IQR]	2 [0 – 3]	2 [1–4]	1 [0 – 3]	< 0.001
Collapse-to-CPR time, min, median [IQR]	3 [0 – 7]	3 [0 – 10]	2 [0 – 5]	0.02
CPR-to-ROSC time, min, median [IQR]	20 [14–30]	21 [15–30]	20 [10–30]	0.0002
Cause of cardiac arrest, n (%): Ischemic cause Cardiac non-ischemic cause Hypoxemic cause Other cause	359 (44) 130 (16) 160 (20) 167 (21)	268 (44) 90 (15) 122 (20) 123 (20)	91 (43) 40 (19) 38 (18) 44 (21)	0.56
Cardiac arrest of ischemic cause vs. other cause, n (%)	359 (44)	268 (44)	91 (43)	0.66
Targeted temperature control, n (%)	699 (86)	519 (86)	180 (85)	0.54
SAPS II score, median [IQR]	68 [57 – 80]	70 [57 – 82]	64 [55 – 75]	< 0.001
Charlson score, median [IQR]	0 [0 – 2]	1 [0 – 2]	0 [0 – 2]	0.09
SOFA score at admission, median [IQR]	10[8–12]	10 [8–12]	9 [7–12]	< 0.001
Initial lactate level, mmol/L, median [IQR]	4.1 [2.1 – 7.5]	4.6 [2.2 – 8]	3.1 [1.7 – 5.8]	< 0.001
Initial pH level, median [IQR]	7.26 [7.15 – 7.34]	7.25 [7.12 – 7.34]	7.29 [7.19 – 7.35]	0.001
Initial hemoglobin level, g/dL, median [IQR]	13.4 [12 – 14.8]	13.4 [11.9 – 14.8]	13.7 [12.2 – 14.8]	0.21
CAHP score, median [IQR]	167 [131 – 199]	173 [137 – 205]	151 [113 – 188]	< 0.001
Maximum SOFA score in first 72 h, median [IQR]	11 [9–13]	11 [9–13]	10 [8–12]	< 0.001
Maximum VIS in first 72 h, µg/kg/min, median [IQR]	41 [14 – 117]	51 [19 – 138]	22 [0 – 57]	< 0.001

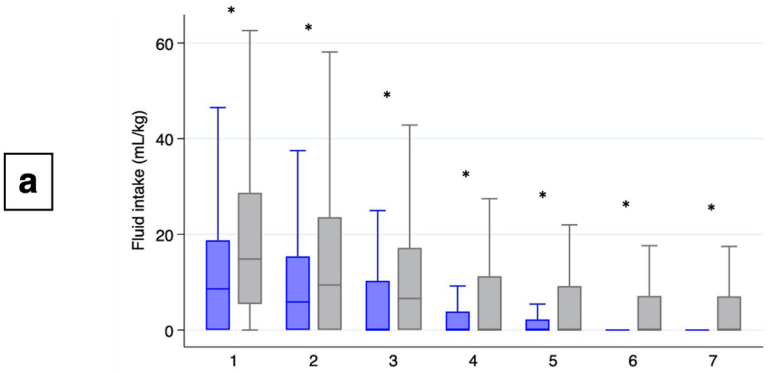
CPR cardio pulmonary resuscitation, *IQR* inter quartile range, *ROSC* return of spontaneous circulation, *SAPS* simplified acute physiology score, *SOFA* sepsis-related organ failure assessment, *VIS* vasoactive inotropic score

breakdown of intake, diuresis, and fluid balance from day 1 to day 7 for survivors and non-survivors. From day 1 to day 7, fluid intake and fluid balance were consistently and significantly higher in non-survivors, while diuresis was significantly lower (except on day 7).

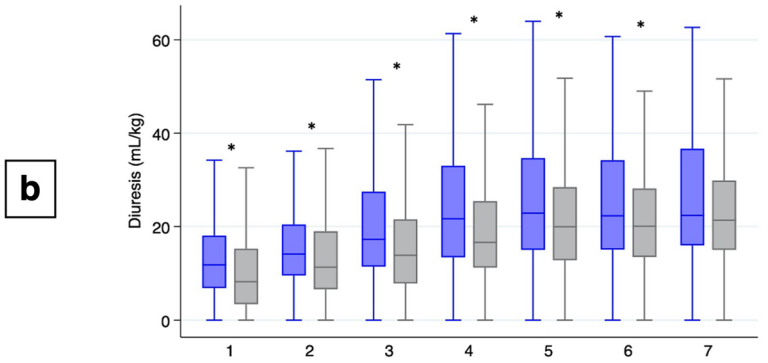
Main outcome

At day 90, 291 of 816 patients (36%) had survived, with 28% survival in patients with a positive fluid balance and 57% survival in patients with a negative fluid balance. Figure 3 shows the Kaplan–Meier survival curve comparing 90-day survival according to fluid balance. In univariate analysis, a positive fluid balance was significantly associated with mortality at day 90 (hazard ratio (HR) = 2.2 [1.7 – 2.7], $p < 0.001$). Univariate and multivariate analyses are shown in Table 2. After adjustment in a multivariate Cox model, a positive fluid balance remained independently associated with mortality (HR = 1.8 [1.3 – 2.3], $p < 0.001$).

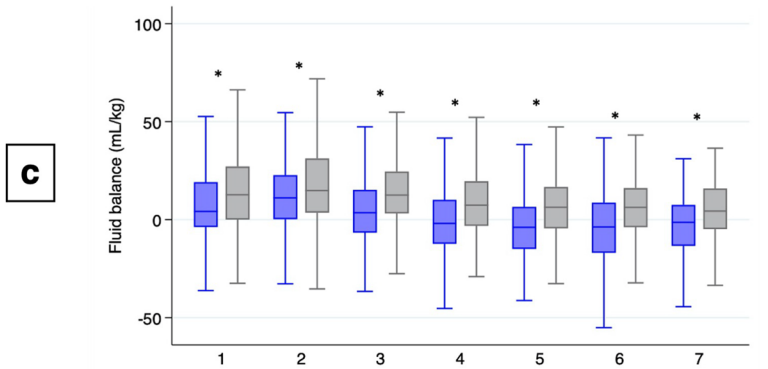
A propensity score was then developed. Variables associated with a positive fluid balance in univariate logistic regression are presented in Supplementary file 2. The logistic model used to estimate the propensity score for a positive fluid balance included bystander witnessed OHCA, time from collapse to CPR, maximum SOFA score in the first 72 h, and maximum VIS in the first 72 h (model C statistic = 0.66). A total of 193 matched pairs of patients (each pair consisting of one patient with a positive and one with a negative fluid balance) were balanced for covariates (Supplementary



	Day	1	2	3	4	5	6	7
Fluid intake (mL)	Survivors	750 [0–1500]	500 [0–1250]	0 [0–1000]	0 [0–475]	0 [0–220]	0 [0–0]	0 [0–0]
	Deceased	1000 [500–2046]	1000 [0–1792]	500 [0–1500]	146 [0–1000]	0 [0–700]	0 [0–500]	0 [0– 500]



	Day	1	2	3	4	5	6	7
Diuresis (mL)	Survivors	965 [565–1400]	1150 [800–1605]	1365 [905–2200]	1700 [1155–2700]	1800 [1150–2750]	1740 [1300–2750]	1800 [1300–2850]
	Deceased	630 [255–1100]	900 [485–1430]	1000 [610–1600]	1292 [820–1830]	1475 [1000–2080]	1460 [1000–2100]	1640 [1125–2300]



	Day	1	2	3	4	5	6	7
Fluid balance (mL)	Survivors	342 [-312–1500]	899 [10–1809]	253 [-562–1220]	-157 [-1063–823]	-320 [-1320–524]	-285 [-1441–645]	-140 [-1114–660]
	Deceased	936 [0–2037]	1179 [250–2299]	991 [206–1800]	567 [-220–1446]	493 [-302–1207]	461 [-307–1152]	360 [-396–1115]

Fig. 2 Fluid intake, diuresis, and fluid balance during the first 7 days after OHCA between survivors and non-survivors at day 90. Legend: survivors are shown in blue, non-survivors in light gray. An asterisk (*) indicates a significant difference between the two groups. **a**: fluid intake in mL/kg, **b**: diuresis in mL/kg, **c**: fluid balance in mL/kg

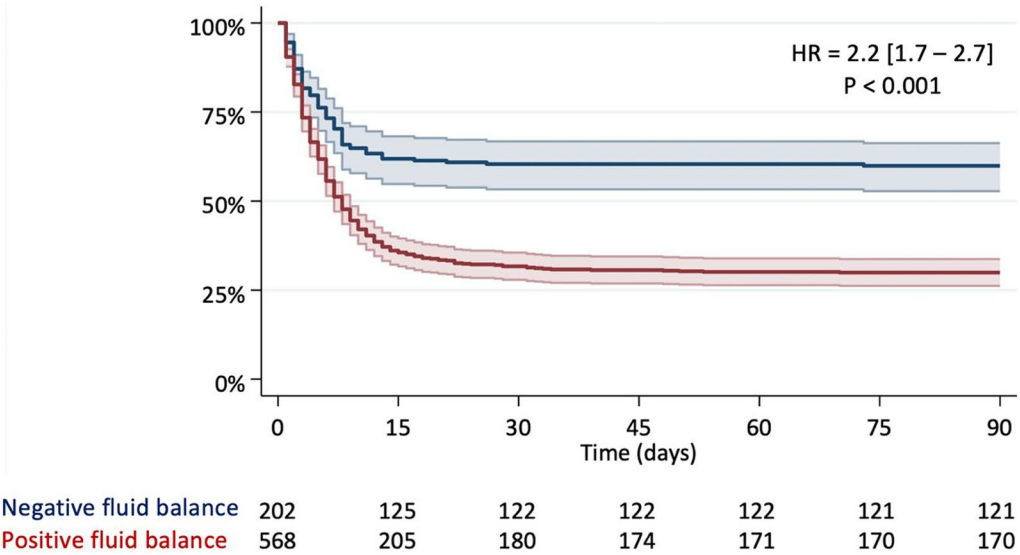


Fig. 3 Kaplan Meier curves representing 90-day survival according to cumulative fluid balance at day-7. Red curve represents patients with a positive fluid balance and blue curve with a negative fluid balance

Table 2 Univariate and multivariate analysis of variables associated with mortality at 90 days

Variable	HR	95% CI	*p*	HR	95% CI	*p*
Age (every year)	1.02	[1.01 – 1.03]	< 0.001	1.02	[1.01 – 1.03]	< 0.001
Male	0.7	[0.6 – 0.9]	0.002			
At home	1.7	[1.5 – 2.1]	< 0.001	1.3	[1.04 – 1.6]	0.02
Bystander-witnessed	0.6	[0.5 – 0.7]	< 0.001			
Bystander CPR	0.5	[0.4 – 0.6]	< 0.001	0.8	[0.6 – 0.97]	0.02
Shockable rhythm	0.4	[0.3 – 0.5]	< 0.001	0.5	[0.4 – 0.7]	< 0.001
Epinephrine administered ≥ 2 mg	2.7	[2.2 – 3.3]	< 0.001	1.5	[1.2 – 1.8]	0.001
Collapse-to-CPR time ≥ 3 min	2.1	[1.7 – 2.5]	< 0.001	1.7	[1.4 – 2.1]	< 0.001
CPR-to-ROSC time ≥ 20 min	1.9	[1.6 – 2.3]	< 0.001	1.5	[1.2 – 1.9]	< 0.001
Cardiac arrest of ischemic cause	0.5	[0.4 – 0.6]	< 0.001	0.7	[0.5 – 0.9]	0.005
Targeted temperature control	0.6	[0.5 – 0.8]	< 0.001			
SAPS II score (every point)	1.03	[1.02 – 1.04]	< 0.001	1.01	[1.01 – 1.02]	0.01
Charlson score (every point)	1.1	[1.1 – 1.2]	< 0.001	1.07	[1.02 – 1.1]	0.007
Initial lactate level > 4 mmol/L	2.8	[2.3 – 3.3]	< 0.001	1.7	[1.3 – 2.0]	< 0.001
Initial pH level (every point)	0.07	[0.04 – 0.12]	< 0.001			
Initial hemoglobin level (every 1 g/dL)	0.94	[0.91 – 0.98]	0.003			
Maximum SOFA score in first 72 h (every point)	1.1	[1.1 – 1.2]	< 0.001			
Maximum VIS in first 72 h ≥ 41 µmol/kg/min	2.2	[1.8 – 2.6]	< 0.001	1.4	[1.1 – 1.8]	0.001
Cumulative positive fluid balance	2.2	[1.7 – 2.7]	< 0.001	1.8	[1.3 – 2.3]	< 0.001

CI confidence interval, *CPR* cardio pulmonary resuscitation, *HR* hazard ratio, *ROSC* return of spontaneous circulation, *SAPS* simplified acute physiology score, *SOFA* sepsis-related organ failure assessment, *VIS* vasoactive inotropic score

file 3 and Supplementary file 4). In a multivariate Cox analysis of these 193 pairs, a positive fluid balance remained independently associated with mortality (HR = 1.6 [1.1 – 2.2], $p = 0.005$) (Supplementary file 5).

Several landmark analyses were conducted, successively excluding patients who died before 24, 48, and 72 h. In each adjusted analysis, a positive fluid balance remained consistently associated with increased mortality: at 24 h

(n = 612) (HR = 1.9 [1.4 – 2.6], $p < 0.001$), 48 h (n = 561) (HR = 2.3 [1.7 – 3.2], $p < 0.001$), and 72 h (n = 508) (HR = 2.5 [1.7 – 3.6], $p < 0.001$), Supplementary file 6.

Subgroup and sensitivity analyses

After dividing the cohort based according to the pre-specified CAHP score subgroups, we analyzed the association between a positive fluid balance and mortality among patients classified as low-risk (CAHP < 150, n = 278, 80 (29%) deaths), medium-risk (CAHP 150–200, n = 281, 206 (74%) deaths), and high-risk (CAHP > 200, n = 181, 179 (99%) deaths). Seventy-six patients were excluded from the CAHP score analysis due to missing data making it impossible to calculate the CAHP score. After adjustment, a positive fluid balance was independently associated with mortality in low-risk (HR = 2.2 [1.2 – 4.1], $p = 0.02$) and medium-risk patients (HR = 2.2 [1.5 – 3.3], $p < 0.001$)). However, this association was not significant in high-risk patients (HR = 0.8 [0.5 – 1.2], $p = 0.23$).

When restricting analysis to patients treated with norepinephrine (n = 670, 82% of the population), a positive fluid balance was independently associated with mortality after multivariate Cox regression (HR = 1.9 [1.4 – 2.5], $p < 0.001$).

When restricting analysis to patients without WLST (n = 325, 40% of the population), a positive fluid balance was independently associated with mortality after multivariate Cox regression (HR = 2.5 [1.2 – 4.9], $p = 0.01$).

Finally, regarding neurological outcome, a positive fluid balance was independently associated with an unfavorable neurological outcome (mRS 4 to 6) at 90 days after multivariate logistic regression (adjusted odd ratio (OR) = 4.1 [2.4 – 6.7], $p < 0.001$).

Dose-dependent association

After dividing the cohort into quartiles based on fluid balance, 90-day mortality increased across quartiles, with a mortality rate of 43% in the first quartile compared to 78% in the fourth quartile (p for trend < 0.001, Supplementary file 7). Kaplan–Meier curves illustrating mortality according to fluid balance quartile are shown in Supplementary file 8, with increasing mortality across quartiles relative to the first quartile (HR = 2.3 [1.7 – 3.0], $p < 0.001$, Supplementary file 9).

Secondary outcomes

The outcome of patients according to fluid balance is shown in Supplementary file 10. During their ICU stay, 62 patients (8%) required renal replacement therapy and the median number of ventilator-free days was 0 [0 – 22]. When comparing patients according to their fluid balance, patients with a positive fluid balance were more likely to receive renal replacement therapy (10% with a positive fluid balance vs. 2% with a negative fluid balance, $p = 0.001$) and had a lower minimum P_aO_2/F_iO_2 ratio in the first seven days (158 [100—225] vs. 180 [121—260], $p < 0.001$).

Discussion

In this multicenter, prospective observational study, 82% of patients admitted after OHCA required vasopressors for shock. The median volume of fluid therapy administered during the first seven days was 2500 ml, resulting in a positive fluid balance in 74% of patients. A positive fluid balance was consistently associated with adverse outcomes (both regarding mortality and unfavorable neurological outcome), across various analytical approaches, including multivariate Cox regression, propensity score matching, landmark analysis, and multiple subgroup analyses. Although observational, this adverse association suggests that a restrictive fluid therapy strategy may be beneficial for post-OHCA patients, pending further interventional studies.

Post-resuscitation shock is common after OHCA, occurring in 50 to 70% of patients(2,18). This mixed shock may include varying degrees of myocardial dysfunction, vasoplegia, hormonal disturbances, and vascular leakage leading to hypovolemia(5,19). Recent guidelines(5) suggest using noradrenaline as the first-line agent(12,20); however, they emphasize the lack of evidence to guide optimal fluid therapy in patients after cardiac arrest. Three small, single-center studies reported that fluid therapy among these patients involved administering 4 to 8 L of fluid given in the initial 24 to 72 h(21–23). However, these studies were conducted 15 to 30 years ago, and the practice of administering large volumes of fluid has come under increasing scrutiny. In our study, the median volume of fluids administered within the first seven days was 2500 ml, notably lower. This result masks significant disparities: while 26% of patients achieved a negative fluid balance by day 7, the majority maintained a positive fluid balance, with a quarter of patients exceeding a fluid balance of 5000 ml over seven days. Such fluid overload has been consistently associated with a poor prognosis in critically ill patients(17,24), including those with sepsis(25), traumatic brain injury(26) and acute respiratory distress syndrome(27). However, to our knowledge, there are currently no data on this association in OHCA patients.

In our study, we found a strong, independent association between positive fluid balance and 90-day mortality after cardiac arrest. After adjustment for confounders known to be independent prognostic

factors after OHCA, patients with a positive fluid balance had a 1.8-fold increase in 90-day mortality. A higher fluid balance may indicate greater patient severity or a greater perceived need for fluid resuscitation(6). Our hypothesis in this study was that patients were likely more severe in the group with a positive fluid balance. This was confirmed in our univariate analysis. To address this potential bias, we performed a propensity-matched analysis, which yielded consistent results and reduced the risk of indication bias. In addition, our subgroup analysis across different severity tertiles, as defined by the previously published CAHP score, showed a similar association between positive fluid balance and mortality in low and medium-risk patients. The lack of a significant association in the most critically ill patients (CAHP score over 200) may be due to the very low survival rate in this subgroup (0–2% in the princeps study(14), 2/181 patients in the present study), which limits the power of this analysis. Another potential source of bias could be related to the temporal sequence of fluid balance, which is typically positive at first and negative later. The sickest patients, who die early, would not have opportunity to reach a negative balance, whereas those who survive for several days may benefit from an immortality bias. However, the stability of our results, even after performing landmark analyses at different time points, addresses this potential bias. The sensitivity analysis using an unfavorable outcome as the endpoint with consistent results, along with a dose-dependent association, further reinforces our findings.

Several pathophysiological hypotheses may explain this negative association. First, myocardial dysfunction is common after OHCA, with varying degrees of severity(19,21,28). In this context, fluid overload may both exacerbate myocardial dysfunction, and be poorly tolerated, therefore worsening prognosis and contributing to increased mortality. Two randomized trials evaluating rapid cold saline infusion during CPR found reduced ROSC rates(29), and an increased risk of pulmonary oedema and re-arrest(30) in patients treated with fluid loading. Second, a positive fluid balance may directly affect neurological function [31, 32], through mechanisms such as exacerbating cerebral oedema, disrupting microcirculation, causing endothelial dysfunction [33], or inducing metabolic imbalances. As a result, ESICM guidelines advocate for maintaining normovolemia in neurocritical patients [34]. Finally, fluid overload and fluid accumulation syndrome [35] are risk factors for organ failure, including acute kidney injury [36] and prolonged mechanical ventilation [6]. These findings align with our results, showing higher rates of renal replacement therapy, fewer ventilator-free days, and longer hospital stays in patients with a positive fluid balance.

We acknowledge several limitations. First, our results are observational, and we cannot establish causality between positive fluid balance and mortality. However, the consistency of results across different methodological approaches, the dose-dependent association, the pathophysiological coherence, and the external validity support this hypothesis, which would require interventional studies to confirm. Second, we cannot completely exclude an indication bias that may lead to higher fluid loading in the sickest patients; however, our propensity score analysis does not support this hypothesis. Third, hemodynamic management was not standardized and may have varied between centers. Nonetheless, given the lack of strict guidelines in this setting, our observational design reflects real-world practices. Fourth, we did not collect data on prehospital fluid administration. However, the 2021 guidelines [37] advise against large-volume fluid infusion, and we can assume that this non-differential bias affects all patients equally. Finally, we were not able to report specific hemodynamic and cardiac echography data such as cardiac index, systemic vascular resistance, or fluid responsiveness.

Conclusions

In this multicenter observational study, a positive fluid balance after OHCA was common, observed in 74% of patients, and was consistently and independently associated with worse outcomes across various analyses. These findings are hypothesis-generating and consistent with the existing critical care literature. Interventional studies comparing conservative versus liberal fluid strategies after OHCA may provide valuable insights.

Abbreviations

CPR	Cardio-pulmonary resuscitation
HR	Hazard ratio
ICU	Intensive care unit
mL	milliliters
OHCA	Out-of-hospital cardiac arrest
OR	Odd Ratio
ROSC	Return of spontaneous circulation
SAPS II	Simplified acute physiology score (SAPS) II
SOFA	Sepsis-related organ failure assessment
VIS	Vasoactive inotropic score
WLST	Withdrawal of life sustaining therapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05391-x.

Supplementary file1

Acknowledgements
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Author contributions
All authors contributed to the study conception, design and data collection. Analysis were performed by MR, WB et AC. The first draft of the manuscript was written by MR and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding
None.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was conducted according to the Strengthening The Reporting of OBservational studies in Epidemiology guidelines, and the cohort was registered on ClinicalTrial.gov before the first patient was enrolled (Cohort AfterROSC-1, NCT04167891 registered November 13th, 2019)(8). The research protocol was approved by the relevant ethics committees (2019-A01378-49; CPP-SMIV 190901) and the French data protection authorities, according to the principles of the Declaration of Helsinki. According to French law, patients or relatives were informed of their inclusion in this study, an information notice was provided to them, and their non-opposition was documented.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 22 January 2025 Accepted: 27 March 2025
Published online: 14 April 2025

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